Reappraisal of the coupling interval of ventricular extrasystoles as an index of ectopic mechanisms

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Abstract

***Objective*—A mathematical model of modulated ventricular parasystole based on the relation between the coupling interval and the preceding RR interval was developed in an attempt to distinguish between parasystolic automaticity and other mechanisms.**

***Mathematical model*—The relation between the coupling interval and the preceding RR interval was examined by plotting the coupling interval of each extrasystole against the preceding RR interval (coupling interval/RR diagram). The coupling interval/RR diagrams obtained from simulations with various modulation modes suggested that the parasystolic mechanism was likely when the dots representing extrasystoles appeared as discrete clusters. In contrast, a linear horizontal accumulation of dots indicated a non-parasystolic mechanism.**

***Clinical observation*—To verify the validity of the simulations, 24 hour electrocardiographic recordings from 60 patients with frequent ventricular extrasystoles (>1000/day) were analysed to determine whether the extrasystoles showed intrinsic periodicity. Intrinsic periodicity indicative of a parasystolic mechanism was seen in 14 (93%) of 15 patients in whom the coupling interval/RR diagram was characteristic of a parasystolic mechanism. When the coupling interval did not change (variability <200 ms) over a wide range of RR intervals (>700 ms) intrinsic periodicity was never identified (0/17). Parasystolic automaticity was the likely mechanism in 11 of the remaining 28 patients (39·3%) in whom coupling interval/RR diagrams were not definitive.**

***Conclusion*—These data indicate that definite patterns of coupling interval/RR diagrams can be used to distinguish between parasystolic and non-parasystolic mechanisms.**

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Experimental and mathematical studies by Jalife and others on modulated parasystole[1–3] suggested a fixed coupling interval between parasystolic premature ventricular complexes and the preceding beat. Subsequent clinical observations[4–6] confirmed that the coupling interval of ventricular parasystole was not always randomly distributed and that both parasystolic and non-parasystolic mechanisms can show similar distributions of coupling intervals. Since then the diagnostic significance of the coupling interval has received little attention.

In a preliminary study in which we plotted the coupling interval of ventricular extrasystoles against the preceding RR interval we found that in some patients the coupling interval was consistent over a wide range of RR intervals. We assumed that a parasystolic mechanism was unlikely in these cases, but without objective evidence. To determine the likely and unlikely relations between the coupling interval and the preceding RR interval in parasystole we developed a mathematical model of modulated ventricular parasystole. The aim of this study was to determine the validity of using the relation between coupling and RR intervals as an index of ectopic mechanisms.

Patients and methods

We defined ventricular parasystole as an independent ectopic ventricular rhythm that has an inherent cycle length and is modulated by electrotonic influences but is not discharged by the dominant rhythm.[7]

MATHEMATICAL MODEL

The four variables in the mathematical simulation were the parasystolic cycle length, sinus cycle length, phase-response curve, and refractory period.

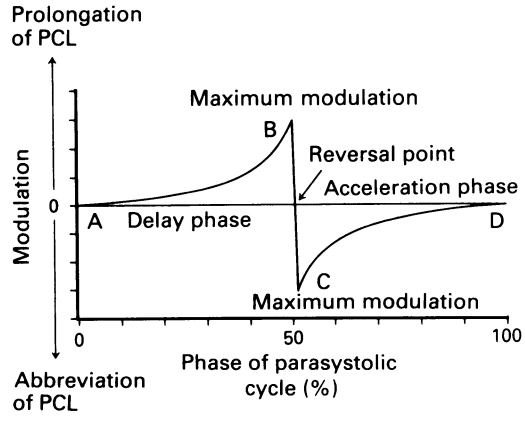

Figure 1 Biphasic phase-response curve for phase of parasystolic cycle (%) where a sinus beat falls and degree of modulation (%) of the parasystolic cycle length. The curve consists of a delay phase (A to reversal point) and an acceleration phase (reversal point to D). The occurrence of sinus beats during the delay phase prolongs the parasystolic cycle length (PCL), whereas during the acceleration phase it shortens the PCL.

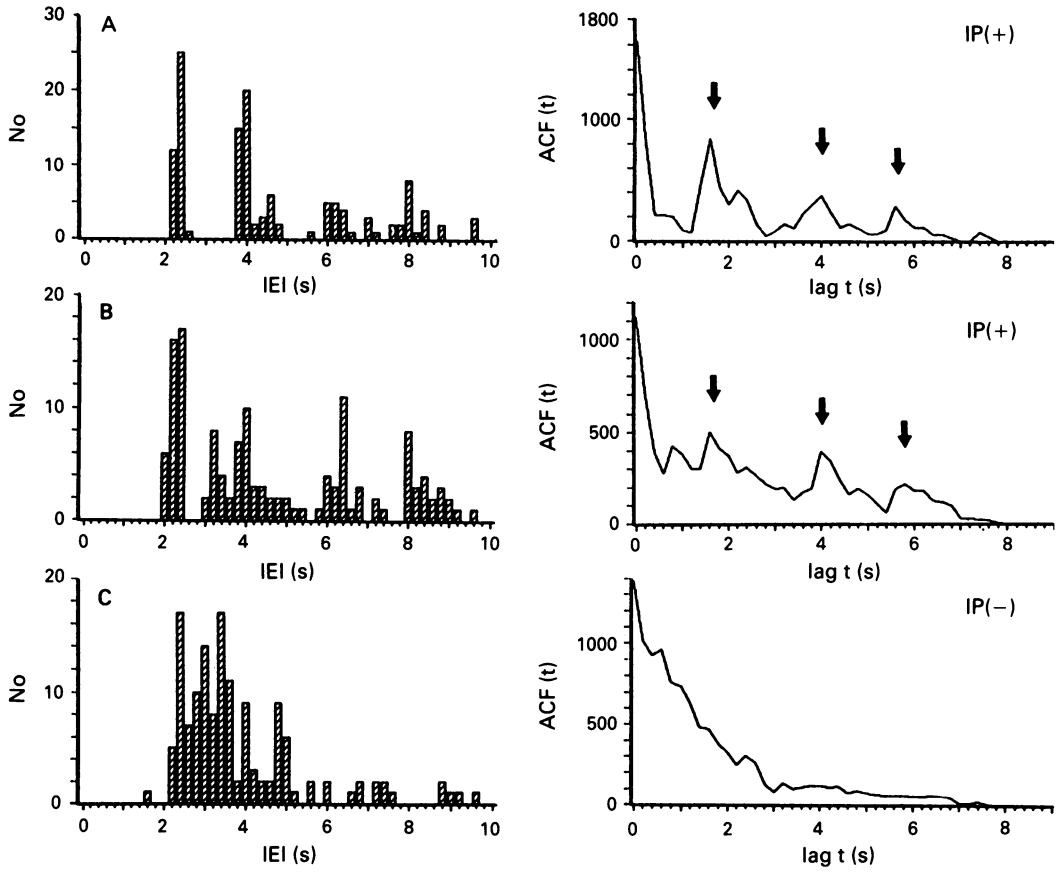

Figure 2 Examples of frequency histograms of inter-ectopic intervals (left) and autocorrelation function (ACF(t)) curves (right) in three patients. The frequency histograms show inter-ectopic intervals (IEI) and number of IEIs for every 0·2 s. The autocorrelation function is derived from the lag value T and the calculated ACF(t). A and B, show intrinsic periodicity (IP) of inter-ectopic intervals. Peaks of ACF(t) that repeatedly appeared at approximately every 2 s indicate inherent periodicity, that is, parasystolic automaticity (panels A and B, right). In panel C there is no inherent periodicity—that is, parasystolic automaticity was not the ectopic mechanism in this patient.

Parasystolic cycle length and sinus cycle length

Sinus and parasystolic discharges were set to start simultaneously at the begininning of simulation and were repeated with electrotonic modulation. The sinus cycle length was set at 400–1150 ms in 50 ms steps, and was shortened or lengthened by up to 20 ms to simulate physiological fluctuations such as respiratory sinus arrhythmia. Originally, the parasystolic cycle length was fixed at 2 seconds. We also tested variable parasystolic cycle lengths, defined as 1·15 × (sinus cycle length) + 1080 ms on the basis of previous clinical observations.[8–10]. For each combination of variables we tested 784 parasystolic cycles.

Phase-response curve

The phase-response curve for modulation of the parasystolic cycle length by the sinus beat was biphasic in earlier biological and clinical studies.[2 4 5] The phase-response curve consists of a delay phase and an acceleration phase separated by the reversal point (fig 1). The degree of maximum prolongation of the parasystolic cycle length was set at 0, 1, 10, 20, 25, or 30% in the delay phase. Maximum shortening in the acceleration phase was set at 0, −1, −10, −20, −25, or −30% of the parasystolic cycle length.[2 4 5] The timing of the reversal point was not specifically defined. Instead, the point corresponding to the maximum prolongation in the delay phase was set as 20–80% of the parasystolic cycle in 10% steps. The distance between the point of maximum prolongation and that of maximum shortening was 1, 10, 20, 30, 40, 50, or 60% of the original parasystolic cycle length. The phase-response curve between the points of maximum modulation was always linear (B-C, fig 1), but the first and third portions (A-B and C-D (fig 1)) were hyperbolic curves or straight lines. The effects of two or more consecutive sinus beats falling during one parasystolic cycle were accumulated stepwise.[1]

Refractory period

The refractory period of exit from the parasystolic focus was estimated as 0·2 × (preceding RR interval) + 200 ms. Only parasystolic discharge outside the period of refractoriness associated with the preceding sinus beat became manifest and thus suppressed the subsequent sinus beat which would have occurred 0·4 × (sinus cycle length) + 100 ms or less after the manifest parasystole. These variables were selected from observations of our cases of apparent parasystole and from earlier reports.[9 10] The influence of parasystole on sinus cycle length was not included in the model because it could not be quantified. The coupling interval of each parasystolic beat was plotted against the preceding RR interval to show the relation between the two variables.

ANALYSIS OF CLINICAL OBSERVATIONS

Description of patients

We selected 60 consecutive 24 hour ambulatory electrocardiographic recordings with frequent ventricular extrasystoles (> 1000 per day). The recordings were excluded if repetitive forms were frequent (couplets, triplets, and short runs > 10% of total episodes), if extrasystoles were so loosely scattered that measurements of inter-ectopic intervals were useless, if there was

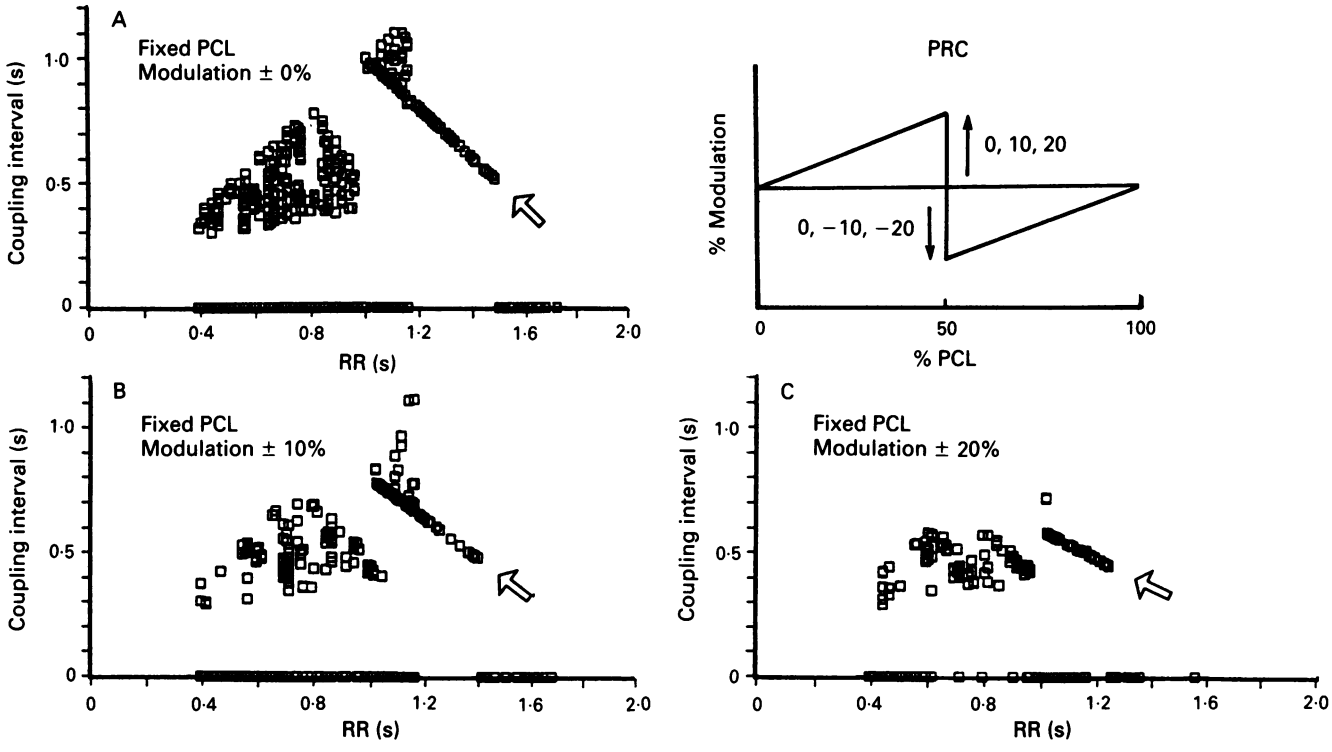

Figure 3 Diagrams of coupling interval/preceding RR interval (RR) acquired from a mathematical simulation of parasystole. The parasystolic cycle length (PCL) was fixed at 2 s. The degree of maximum modulation was set at ±0% (A), ±10% (B), and ±20% (C). Maximal modulation was set to occur at 50% and 51% of parasystolic cycle length. Each dot represents a single parasystolic complex. Dots on the abscissa—that is, coupling interval = 0—are discharges concealed by the refractory period of the preceding sinus beat. The dots were distributed as a cluster (left) and a linear cluster (arrow). PRC, phase-response curve.

atrial fibrillation or frequent premature supraventricular extrasystoles, or if the sinus cycle length varied by more than 400 ms.

We studied 30 men and 30 women aged 15–85 (mean (SD) 57·3 (13·7)). Three patients had dilated cardiomyopathy, three coronary artery disease, and two variant angina. Mitral valve prolapse was seen in one. Routine clinical examinations including echocardiography did not show organic heart disease in the remaining 51.

The 24 hour electrocardiographic recordings were analysed by computer (SCM 280, Fukuda Denshi, Tokyo, Japan). The coupling interval of each extrasystole was automatically plotted against the preceding RR interval. Extrasystoles with QRS configurations other than the dominant form were excluded from analysis. The likelihood of a parasystolic or non-parasystolic mechanism in each patient was assessed on the basis of the results of the mathematical model.

Evaluation of parasystolic automaticity

The diagnosis of parasystolic automaticity was based on the intrinsic periodicity in the appearance of extrasystoles. One hundred or more consecutive inter-ectopic intervals (<15 s) were measured during stable sinus rhythm (variation < 10 per minute). Frequency histograms of the inter-ectopic intervals were constructed for every 200 ms [I(x) = incidence of inter-ectopic intervals between x seconds and x + 0·2 seconds]. To determine periodicity, the autocorrelation function ACF(t) was calculated by the following formula:

$$ACF(t) = \sum_{\kappa=0}^{75} [I(0{\cdot}2k) \times I(0{\cdot}2k+t)],$$

where t is the lag of the autocorrelation function.[11] From the upper limit of the summation, it can be seen that as lag t increases, the number of samples available for calculation decreases. This leads to a reduction in the magnitude of ACF peaks as t increases. Figure 2 shows examples of frequency histograms of inter-ectopic interval and the corresponding ACF(t). Periodic peaks of ACF(t), which were independent of sinus cycle length (fig 2A and B), were diagnostic of parasystole.

STATISTICAL ANALYSIS

Data are presented as means (SD). Differences in proportions were analysed by the generalised χ^2 test. The unpaired *t* test was used to compare mean values. A probability (p) value <0·05 was regarded as significant.

Results

MATHEMATICAL MODEL

Figures 3–5 are examples of coupling interval/RR diagrams simulated with the mathematical model of parasystole. Figure 3 shows the effects of the degree of modulation on the relation between the two variables with a fixed parasystolic cycle length. When the parasystolic cycle length was independent of sinus discharge—

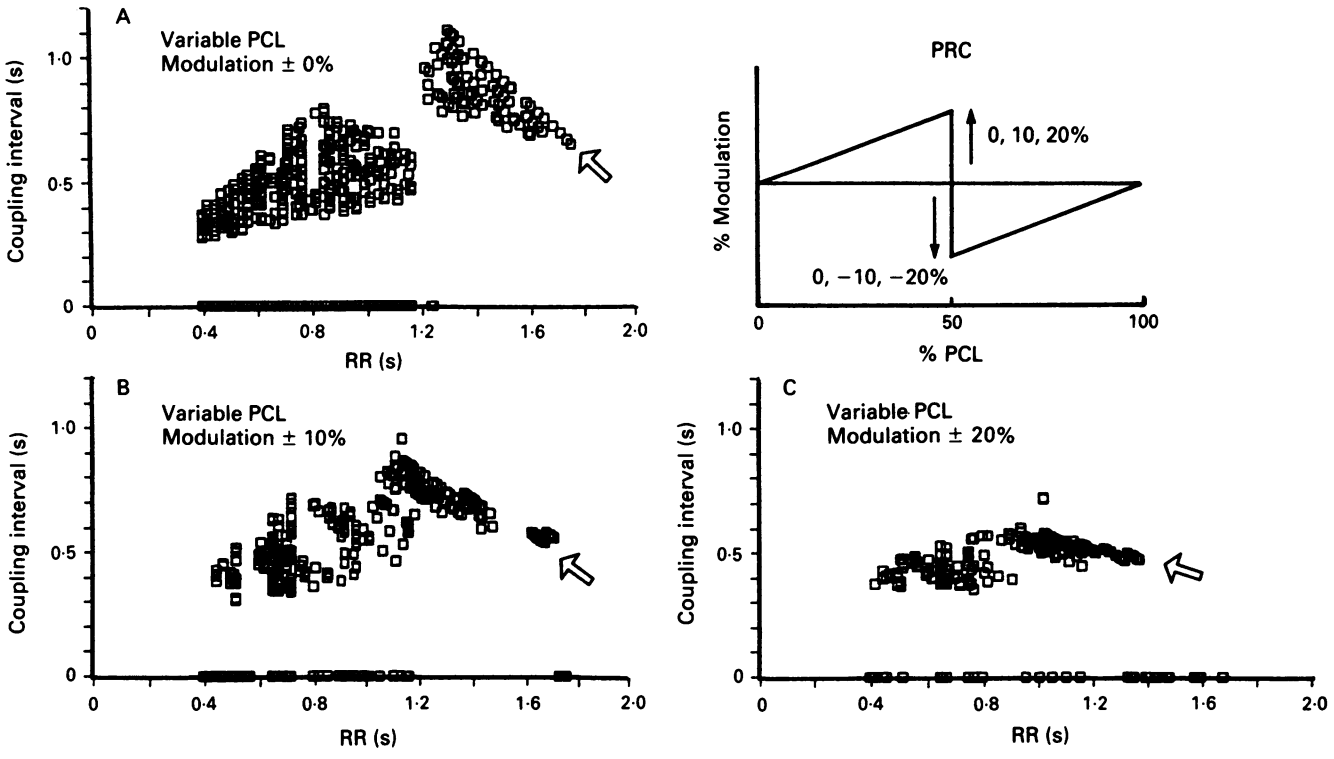

Figure 4 Coupling interval/RR diagrams acquired from the mathematical simulation of parasystole with variable parasystolic cycle lengths (1·15 × (sinus cycle length) + 1080 ms). The degree of maximum modulation is indicated. Maximal modulation was set to occur at 50% and 51% of parasystolic cycle length. The cluster of dots on the right hand side remained (arrows). See legend to fig 3 for abbreviations.

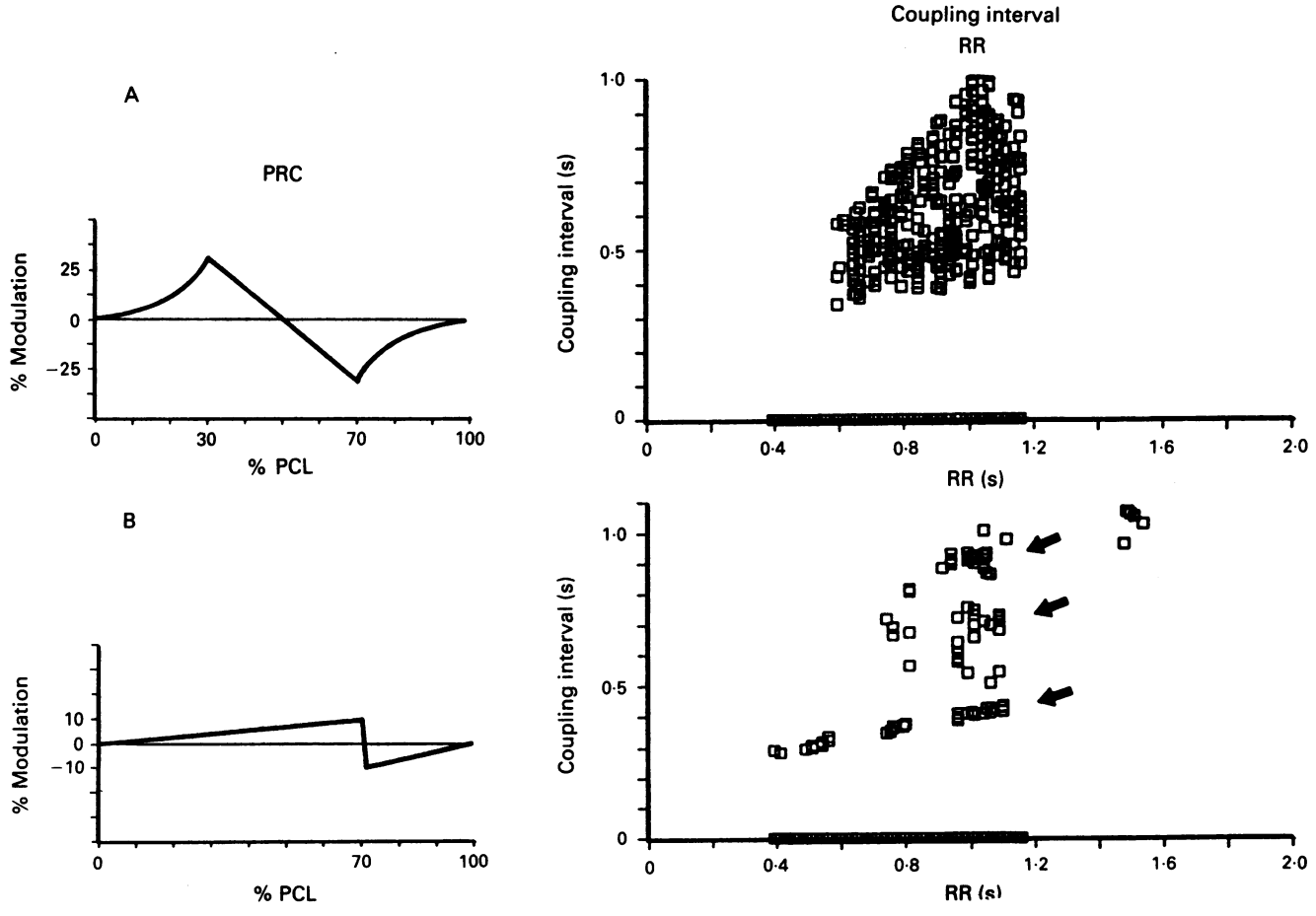

Figure 5 Coupling interval/RR diagrams from the mathematical models with different phase-response curves (PRC). (A) a coupling interval/RR diagram without a dot-free space, (B) an example in which the coupling intervals clustered around three values (0·4, 0·7, and 0·9 s) (arrows). See legend to fig 3 for abbreviations.

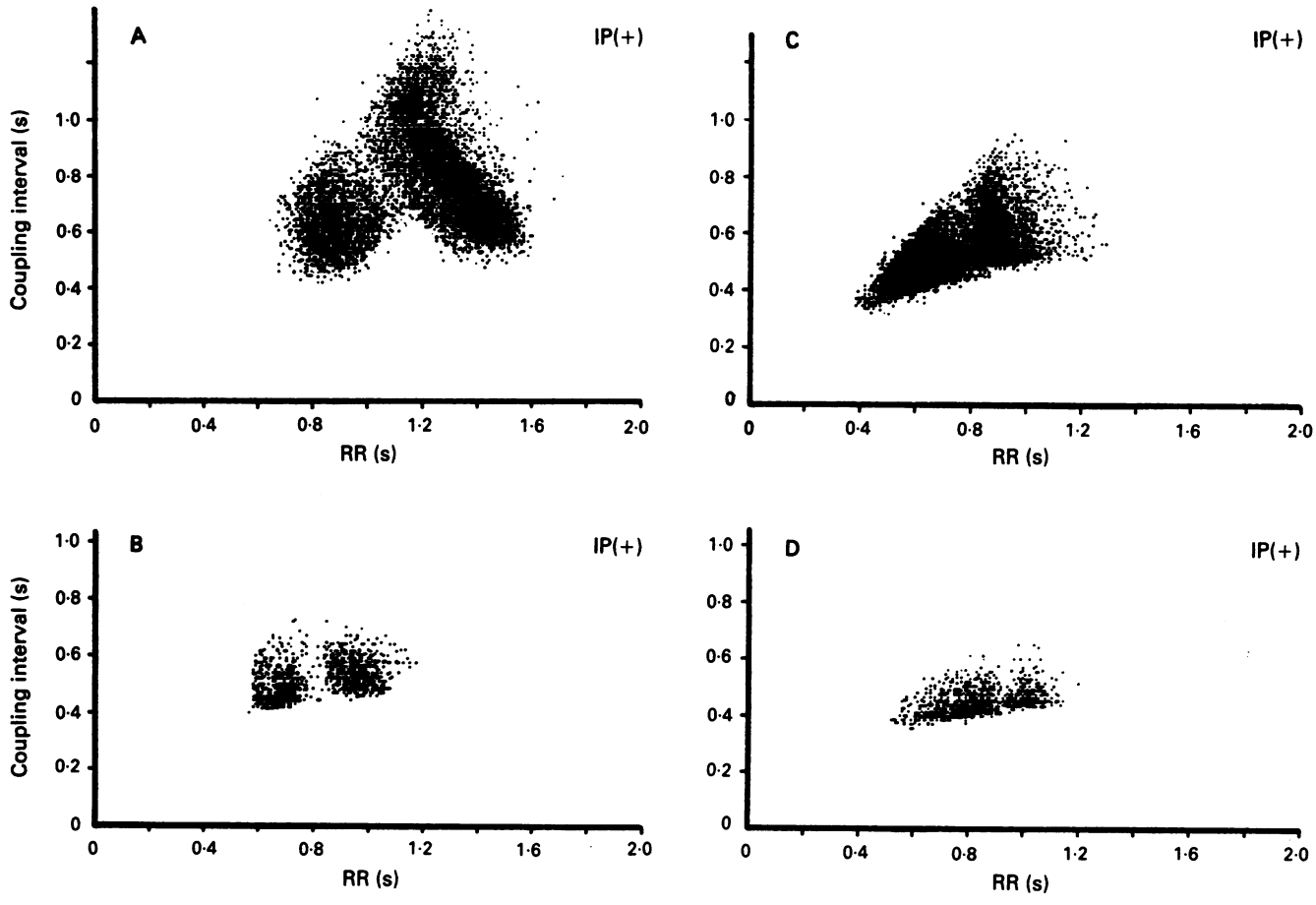

Figure 6 Examples of relation between the coupling interval and the preceding RR interval obtained from 24 hour electrocardiographic recordings from four type 1 patients. There was evidence of intrinsic periodicity (IP) of extrasystoles in all 4. Figure 2A shows the frequency histogram of interectopic intervals corresponding to fig 6C. See legend to fig 3 for abbreviations.

that is no modulation—the coupling interval/RR diagrams showed a linear concentration of dots (arrow, fig 3A). Because the sum of the coupling and RR intervals that constituted this linear accumulation was equal to the parasystolic cycle length (2 s), it was apparent that these dots were associated with an ectopic-sinus-ectopic sequence with a compensatory pause. Although the slope and length gradually changed with changes in modulation, a right-sided linear accumulation remained (fig 3B and C). More extensive modulation—that is +25 to −25% or more, concealed most of the parasystolic discharge (not shown).

Figure 4 shows the effect of a variable parasystolic cycle length on the relations between coupling interval and RR interval. A linear diagonal accumulation of dots was present whatever the degree of modulation (arrows). The distinguishing difference in the coupling interval/RR diagrams between fixed (fig 3) and variable (fig 4) parasystolic cycle lengths was the density of dots along the diagonal.

Coupling interval/RR diagrams without a linear concentration of dots were rarely obtained except with certain phase-response curves (fig 5A). As in the earlier study[2] coupling intervals clustered at two or three widely separated positions with some phase-response curves (fig 5B). However, this distintive distribution of dots was exceptional and disappeared with only slight modification of the phase-response curve.

Thus by arranging the variables of the model various coupling interval/RR diagrams could be produced. However, a horizontally linear accumulation of dots over a wide range of RR intervals, corresponding to a consistent coupling interval, was not seen.

APPLICATION OF OBSERVATIONS IN THE MATHEMATICAL MODEL TO THE DIAGNOSIS OF ECTOPIC MECHANISMS OF CLINICAL ARRHYTHMIAS

Extrapolating the observations in the model to clinical arrhythmias, we considered that a parasystolic mechanism was likely when dots appeared as two or more clusters separated by dot-sparse areas. There are dot-sparse spaces in the left-sided cluster in fig 3A and 3B and fig 4A, B, and C. However, because the occurrence and sites of these dot-sparse spaces were not constant, we did not regard this observation as a characteristic of the parasystolic mechanism.

CLINICAL OBSERVATIONS

Clinical ventricular extrasystoles were divided into three groups.

Type 1—when dots in the coupling interval/RR diagram were divided by dot-sparse space(s) parasystolic automaticity was considered to be the mechanism involved. Figure 6 shows examples of this type. Fifteen patients

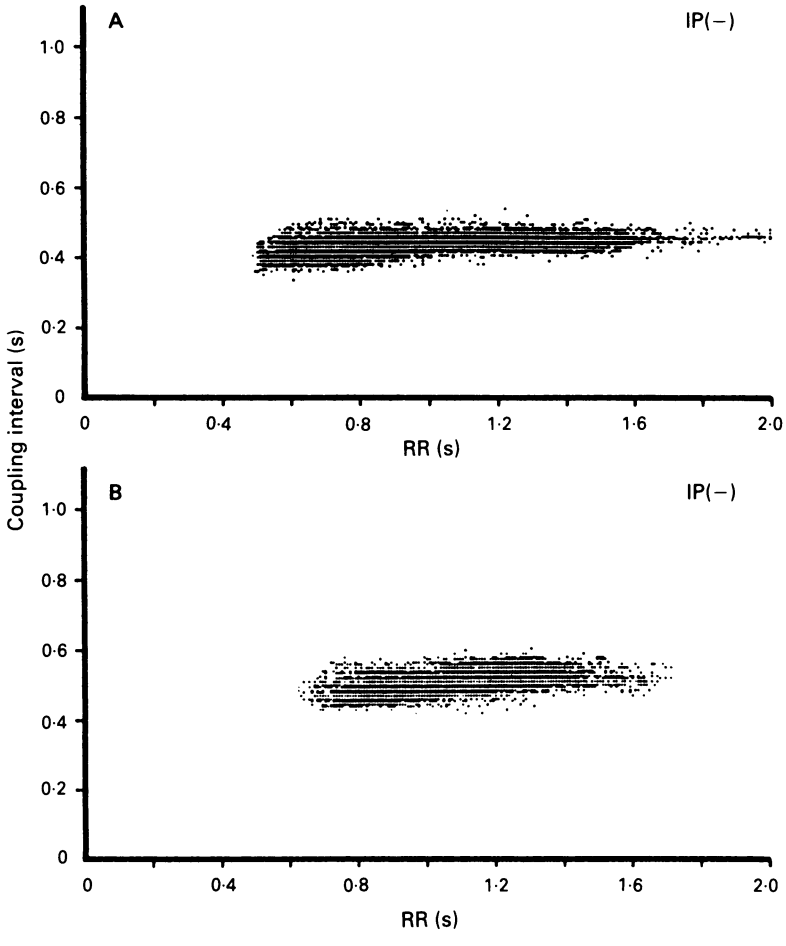

Figure 7 Coupling interval/RR diagrams from type 2 patients in which there was no intrinsic periodicity (IP) of the extrasystoles. The horizontal linear clustering was unique to this group. See legend to fig 3 for abbreviations.

had a distinctive distribution of this type. In 14 (93%) of these 15 recordings we saw intrinsic periodicity of the extrasystoles that was suggestive of parasystolic automaticity. The possible parasystolic cycle length ranged from 1·5 to 2·7 s (2·0 (0·3) s). In the remaining recording, inter-ectopic intervals clustered around three and six seconds but not around nine seconds. The diagnosis of parasystolic automaticity was not definite in this case.

Type 2—If there was a horizontal accumulation of dots over a wide range of RR (> 700 ms) non-parasystolic mechanisms were considered to be the most likely cause of the extrasystoles (fig 7). Seventeen patients had plots of this type. Intrinsix periodicity of extrasystoles was never seen in this group.

Type 3—The remaining 28 patients make up a third group (fig 8). Because the clusters of dots were divided into upper and lower groups but not into right and left ones in fig 8B, this diagram was not considered specific for the parasystolic mechanism. The extrasystoles in fig 8C were diagnosed as parasystolic automaticity, while those in figs 8A and B were not. Frequency histograms of the inter-ectopic interval and ACF(t) indicated parasystolic automaticity as the mechanism of the extrasystoles in 11 (39%) of these 28 patients. The possible parasystolic cycle length ranged from 1·5 s to 3·0 (2·0 (0·4)) s (not significant compared with type 1).

Inter-group differences in the incidence of intrinsic periodicity were significant ($p < 0·0001$).

Discussion

INTERPRETATION OF RESULTS

Both parasystole and reentrant extrasystoles can show fixed coupling to the preceding beat.[2 4 9] In an experimental study triggered activity caused bigeminy with fixed coupling.[12] Therefore, analysis of the coupling interval alone seems of limited value in determining the underlying mechanisms. In our study, an extremely high incidence of intrinsic inter-ectopic periodicity was shown in type 1 patients. Type 2 patients did not show such periodicity. Neither the relation between coupling and RR intervals nor the measurement of the interval between extrasystoles provided a definite diagnosis of the ectopic mechanisms. However, the coupling interval/RR diagram was an accurate indicator of parasystolic and of non-parasystolic mechanisms in patients with type 1 or type 2 patterns: the diagnoses based on the two methods were the same in 31 of the 32 patients.

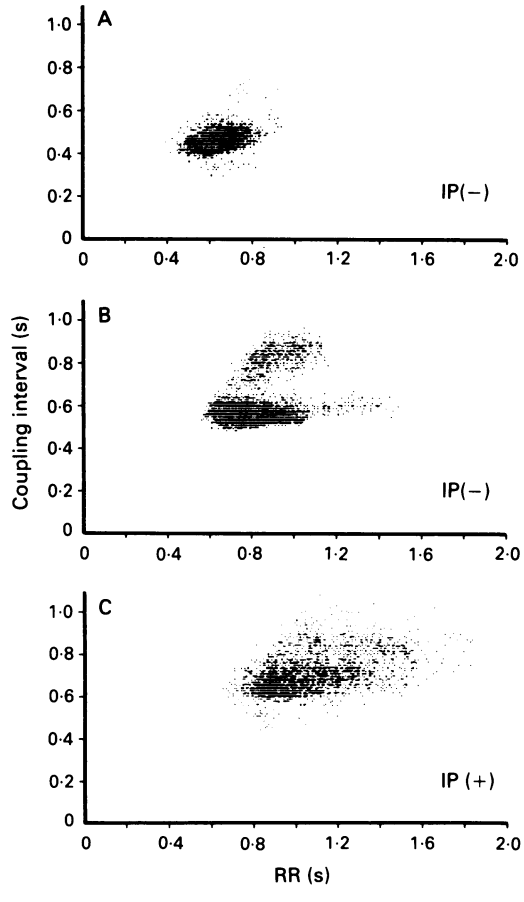

Figure 8 Coupling interval/RR diagrams from type 3 patients. There was intrinsic periodicity (IP) of extrasystoles in patient C. Figure 2C is the frequency histogram of inter-ectopic intervals for patient A and fig 2B is the frequency histogram for patient C. See legend to fig 3 for abbreviations.

Michelson *et al* found that the response of the coupling interval to changes in sinus cycle length induced by exercise was not uniform even if coupling was temporarily fixed.[13] The incidence of parasystolic automaticity in their study was smaller than that in the present study (10% *v* 43·3%). Differences in the number of extrasystoles analysed, in the range of sinus cycle lengths, and in the definition of parasystole may explain this discrepancy. Nevertheless, both their results and ours showed that the relation between the coupling and RR intervals indicated the ectopic mechanism.

EXPLANATION OF RESULTS

Moe *et al* reported stable entrainment of parasystolic ventricular extrasystoles causing bigeminy and trigeminy in a mathematical model.[2] The ultimate pattern was the same irrespective of the starting condition. Also, they found that the coupling interval clustered at long or short intervals, even if it was not fixed in a strict sense. These observations indicated that the range of coupling intervals in parasystole is inherently determined by the combination of sinus and parasystolic cycle lengths and by the mode of modulation.

Figure 3 indicates that the ectopic-sinus-ectopic sequences that usually appeared as bigeminal group beating might generate an additional cluster of dots at RR intervals longer than 1·15 seconds. The degree of modulation may be reflected in the slope of this right-sided linear, diagonal cluster. Clearly, the sum of the coupling interval and RR for the ectopic-sinus-ectopic sequences is identical to the parasystolic cycle length (2 s) when modulation is absent. When modulation is present, the slope of right-sided linear accumulation tends to be less steep. This may be because the degree of shortening of parasystolic cycle length correlates negatively with RR, making the sum of the coupling interval and RR greater at a longer RR when the sinus beat occurs predominantly in the acceleration phase of the parasystolic cycle during bigeminal group beating.

METHODOLOGICAL CONSIDERATIONS

The modulation mode varies from patient to patient.[4 5 9] Oreto *et al* reported a more complex modulation—ie, the triphasic phase-response curve.[14] If the correlation beteen parasystolic and sinus cycle lengths is more linear than we estimated, consistently fixed coupling would be possible. Because the number of combinations of variables was limited in the present study, we cannot exclude the possibility of other types of relations between coupling and RR intervals. The influence of intervening parasystole on sinus rhythm was not included in our model. If a two-way interaction between parasystolic and non-parasystolic complexes is important our results would be affected.

The method used here to detect parasystolic automaticity is not an established one. Although we believe that the autocorrelation function ACF(t) made the intrinsic periodicity of extrasystoles apparent, parasystolic automaticity might sometimes have been overlooked or overdiagnosed.

Finally, our criteria for the diagnosis of parasystole and non-parasystole from the coupling interval/RR diagram were not quantitative. Complicated criteria do not seem to increase the diagnostic sensitivity, because non-specific relations between the two variables, as shown in fig 8, are not infrequent. Further studies are needed to establish a simple criterion that gives excellent sensitivity as well as excellent specificity.

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